DRAFT **MINI MEMO**

TO: Paul Gosselin

FROM: Jay Schreider
John Ross

DATE: May 17, 1999

SUBJECT: Toxicity Endpoints for Pesticides to be Monitored in Lompoc

Per your instructions, we examined the readily available information in order to identify toxicity endpoints and levels to be used for screening the results of the air monitoring in Lompoc. The suggested critical no observable effect levels (NOELs) are in bold.

General Comments

The chemicals examined are alachlor, chlorothalonil, chlorpyrifos, diazinon, dimethoate, disulfoton, fenamifos, fonofos, MITC, methyl bromide, oxydemeton methyl, and permethrin. Since a full toxicity evaluation of the pesticides was neither feasible nor appropriate, the goal was to identify already generated values. The hierarchy was Risk Characterization Documents > Registration Eligibility Documents > Department of Pesticide Regulation (DPR) Toxicology Summaries > August 6, 1998 U.S. EPA Food Quality Protection Act safety factors document > Housenger memorandum > Integrated Risk Information System data. The confidence in a data source increased with the availability of the original data and the thoroughness with which DPR has reviewed the data. Unfortunately, the task did not turn out to be simple or clear cut. No single source of information provided endpoints and toxicity values for acute, subchronic, and chronic exposure for all the pesticides. In some cases, the available documents were in draft form or were only summaries of toxicity, rather than determinations of critical effects and NOELs. In some cases, there were differences between sources of information.

> Risk Characterization Documents (RCDs): RCDs were not available for all the pesticides. A number of RCDs were not final, but did provide thoroughly reviewed toxicity endpoints. Some of the draft RCDs had been released in some form, but others had not. Some of the completed RCDs were old enough that significant new information had been generated.

Reregistration Eligibility Documents (REDs): The only relevant RED that was available was for alachlor; however, it has not yet been finalized by U.S. EPA.

Toxicology Summaries: These DPR summaries provide a listing of the mandatory health effects studies that have been reviewed by DPR scientists, but do not always cover other study types, such as acute or subchronic toxicity. The complete studies are on file at DPR. The use of this document can not substitute for the hazard identification stage of the risk assessment, in which these data are considered along with other relevant data to determine the most scientifically appropriate critical effects. A default approach can be used in which the developmental toxicity studies are used to generate the acute NOELs, the reproduction studies are used for subchronic toxicity, and the lowest NOELs from acceptable chronic toxicity studies are used for the chronic value.

U.S. EPA Safety Factor Document: On August 6, 1998 U.S. EPA released a document addressing the need for additional Food Quality Protection Act (FQPA) safety factors for individual organophosphates. This document lists NOELs for rat developmental toxicity, rabbit developmental toxicity, and rat reproduction studies. Descriptions of individual studies were less detailed than in the DPR Toxicology Summaries.

Housenger Memo: The memo from Jack Housenger of U.S. EPA to Paul Gosselin only covers four pesticides, one of which is not on the monitoring list. In addition, the memo only lists the NOELs, with no ancillary information, such as toxicity endpoint or study type, making review by another agency (Department of Health Services, Office of Environmental Health Hazard Assessment) difficult.

Integrated Risk Information System (IRIS): Toxicity profiles were available for many, but not all of the pesticides. A critical endpoint was only determined for chronic toxicity, which was used as the basis for generating a reference dose (RfD). Thus, these would be the only "official" values. Other

studies (developmental toxicity, reproduction, etc.) are often listed, but no determinations are made. IRIS also tends to reflect the information in the U.S. EPA Office of Pesticide Program's RfD tracking report and the same description would apply. The information provided in these profiles are somewhat less detailed and complete than the DPR Toxicology Summaries.

Specific Chemicals

Alachlor

C A 1989 RCD was completed for alachlor and only evaluated chronic toxicity. The critical NOEL used was 3 milligrams per kilogram (mg/kg) from a dog study with an adjusted NOEL of 2.1 mg/kg (to account for absorption). Alachlor was classified as a carcinogen and maximum likelihood estimate (MLE) and upper bound (UB) potency values of 5.85×10^{-3} and 9.75×10^{-3} respectively were generated in the RCD.

C The Toxicology Summary presents the developmental toxicity study NOEL of 150 mg/kg and the **reproductive toxicity study NOEL of 10 mg/kg**. The chronic NOELs of 0.5 mg/kg for nasal pathology in the rat and the NOEL of 1.0 mg/kg from the dog study are presented.

C We just received a 1998 draft RED from EPA. In the RED, a critical **acute** value of **150 mg/kg** is established from a rat and rabbit developmental toxicity studies for maternal toxicity. The RED used a NOEL of 50 mg/kg from a 21 day dermal toxicity study for subchronic toxicity. A **chronic** NOEL of **1 mg/kg** was generated from a chronic dog study (for mild anemia and mild liver toxicity). Alachlor was treated as a threshold carcinogen, so potency values were not generated. The point of departure for **cancer** was **0.5 mg/kg** for nasal tumors in a rat feeding study.

C In the IRIS document (1993), the chronic RfD of 0.001 mg/kg was set based on a NOEL of 1 mg/kg for hematological effects in a dog study. A NOEL of 10 mg/kg was described for a rat reproduction study for kidney effects and a low effect level (LEL) of 5 mg/kg was described for systemic toxicity in a 6

month dog study. Cancer was not addressed.

Chlorothalonil:

C A draft RCD on chlorothalonil is dated June, 1998. This RCD is not finalized; however, the hazard identification section was sent to the U.S. EPA Science Advisory Panel (SAP), making it a public document. For the powder formulation, the estimated acute inhalation NOEL was 0.032 mg/kg (adjusted to 0.016 to account for 50% inhalation absorption) for pulmonary irritation from a lowest observable effect level (LOEL) air concentration of 0.00208 milligrams per liter (mg/L) in a rat study. For the liquid formulation, the **estimated acute inhalation NOEL was 0.07 mg/kg** (adjusted to 0.035 to account for 50% inhalation absorption) for pulmonary irritation adjusted from a LOEL air concentration of 0.0109 mg/L in a rat study. The acute dermal NOEL was 250 mg/kg (adjusted to 12.5 mg/kg to account for a dermal absorption rate of 5%). The acute oral NOEL was set at 30 mg/kg (adjusted to 10.2 mg/kg to account for an oral absorption rate of 34%). The subchronic inhalation NOELs were derived by applying a factor of 10 to the above acute NOELs. The subchronic dermal NOEL was 60 mg/kg from a 21 day study (adjusted to 3.0 mg/kg using the 5% dermal absorption factor). The subchronic oral NOEL was set at 1.5 mg/kg (adjusted to 0.5 mg/kg using the 34% oral absorption factor). The chronic NOEL was set at **1.8 mg/kg** for non oncogenic kidney lesions in a chronic oral rat study and adjusted by 34% absorption). Based on kidney tumors, MLE and **UB potency factors** of 2 x 10^{-3} and **2.9×10^{-3}**, respectively, were derived. Based on comments from the SAP and on information submitted by the registrant, the argument is being made that chlorothalonil should be treated as a threshold carcinogen.

Chlorpyrifos:

C A dietary RCD for chlorpyrifos was completed in 1992. This document did not derive a subchronic value. The **acute oral NOEL** was set at **0.5 mg/kg**

based on a lack of clinical signs in a single dose oral human study. There was plasma cholinesterase depression at this dose. The **chronic oral NOEL** was set at **1.0 mg/kg** based on depression of brain cholinesterase in rats and dogs. In these studies, the NOELs for depression of red blood cell (RBC) cholinesterase in the rat and dog were 0.12 mg/kg and 0.03 mg/kg, respectively.

C The Toxicology Summary also gives a NOEL of 0.1 mg/kg for plasma and RBC cholinesterase inhibition, and a **NOEL of 1.0 mg/kg** for brain cholinesterase inhibition and reproductive effects in a **rat reproduction** study. In a 13-week rat neurotoxicity study, the NOEL for functional observational battery (FOB) effects is 10 mg/kg. In a rat developmental toxicity study, the NOEL for maternal cholinergic effects is 3.0 mg/kg, and the NOEL for RBC and plasma cholinesterase inhibition is 0.1 mg/kg. In an acute rat neurotoxicity study, the NOEL for neurotoxic effects in the FOB study is 10.0 mg/kg.

C An IRIS toxicity profile set an oral RfD of 0.003 based on a NOEL of 0.03 mg/kg for depression of plasma cholinesterase in a 20 day human study. Presumably, U.S. EPA would also use this value for a subchronic toxicity. This document also noted a chronic NOEL of 0.01 mg/kg for plasma and 3.0 mg/kg (other effects) in a chronic dog study, a NOEL of 0.1 mg/kg for plasma and 3.0 mg/kg (other effects) in a chronic rat study, and a NOEL of 0.1 mg/kg for plasma and 15 mg/kg (developmental effects) in a rat study.

C In the August 6, 1998 document U.S. EPA lists a NOEL of 0.1 mg/kg for maternal plasma and RBC inhibition and 0.5 mg/kg decreased weight gain in a rat developmental toxicity study and a NOEL of 0.1 mg/kg for plasma and RBC cholinesterase inhibition and 0.8 mg/kg for decreased weight gain in a rat reproduction study.

C It is important to note that DPR and U.S. EPA differ in their view of cholinesterase inhibition. DPR generally considers plasma and RBC cholinesterase inhibition indicative of exposure, not adverse effects. On the other hand, U.S. EPA considers plasma cholinesterase inhibition indicative of

either an adverse effect or a surrogate for other more subtle neurotoxic effects that current studies do not measure. These differences become very apparent for chlorpyrifos, where there is such a wide divergence between plasma cholinesterase inhibition and other measured effects.

Cycloate:

- An RCD was completed by DPR on December 8, 1995. The RCD used the critical **acute NOEL** of **20 mg/kg** for **neuronal cell necrosis in the brain** in a single dose oral **rat** study. This NOEL was estimated from a LOEL of 200 mg/kg using a default uncertainty factor of 10. For subchronic inhalation exposure, the RCD used a **NOEL of 0.12 milligrams per cubic meter (mg/m^3) (approximately 0.01 mg/kg)** for **nasal epithelial hyperplasia** from 15 exposure-day **rat** whole body exposure study. This NOEL was estimated from a LOEL of 1.2 mg/m^3 using a default uncertainty factor of 10. The RCD also included a subchronic NOEL of 0.02 mg/kg for neurotoxicity in a 15 exposure-day rat nose-only exposure study (also derived from a LOEL using a default uncertainty factor of 10). Since the former subchronic NOEL was the lowest of the two, it was used to derive the screening level. The RCD used a **chronic NOEL of 0.5 mg/kg for neuromyopathy** from a **rat** chronic oral feeding study and **neurotoxicity** from a **dog** chronic oral gavage study.

Diazinon:

C In 1994 an abbreviated risk assessment was prepared for the use of diazinon in the Mediterranean fruit fly eradication project. This assessment did not evaluate chronic toxicity. "Short term" exposure was evaluated based on a NOEL of 5 mg/kg for clinical signs of cholinergic effects in miniature swine.

C The Toxicology Summary identifies a NOEL of 20 mg/kg from a rat developmental toxicity study for maternal toxicity (decreased weight gain and food consumption) and developmental toxicity. The summary identifies a **LOEL of 2.5 mg/kg** in a **rat acute neurotoxicity study**, which with a 10x uncertainty factor for conversion to a NOEL would be 0.25 mg/kg. The

summary identifies a LOEL of 10 parts per million (ppm) (0.5 mg/kg) for reproductive effects in a reproduction study. The summary identifies a **NOEL of 0.3 ppm (0.015 mg/kg) for inhibition of brain cholinesterase activity in a rat 90 day neurotoxicity feeding** study. The summary identifies a NOEL of 0.1 ppm (0.01 mg/kg) ppm for plasma cholinesterase inhibition, a NOEL of 1.5 ppm (0.15 mg/kg) for RBC and brain cholinesterase inhibition, and a NOEL of 250 ppm (25 mg/kg, highest dose tested) for clinical signs in a rat chronic feeding study. The summary identifies a NOEL of 0.1 ppm (0.0032 mg/kg) for plasma cholinesterase inhibition, and a **NOEL of 0.5 ppm (0.02 mg/kg) for decreased RBC and brain cholinesterase and other effects in a chronic dog study**. It should be noted that the next higher dose was 150 ppm (4.5 mg/kg).

C In the August 6, 1998 document, U.S. EPA lists a NOEL of 20 mg/kg for maternal toxicity in a rat developmental toxicity study and a NOEL of 0.67 mg/kg for decreased weight gain in a rat reproduction study.

Dimethoate

C The toxicology summary lists a **NOEL of 6 mg/kg for maternal toxicity (cholinergic signs) in a rat developmental toxicity study, a NOEL of 1.0 ppm (0.05 mg/kg) for cholinesterase inhibition (plasma, RBC and brain), clinical signs and reproductive effects (decreased fertility) in a rat reproduction study, a NOEL of 1 ppm (0.1 mg/kg) for brain cholinesterase inhibition in a rat chronic study**, and a LOEL of 5 ppm (about 0.0125 mg/kg) for brain cholinesterase inhibition in a chronic dog study.

C In the August 6, 1998 document, U.S. EPA lists a NOEL of 3.0 mg/kg for maternal toxicity in a rat developmental toxicity study and a NOEL of 0.08 mg/kg for decreased weight gain in a rat reproduction study.

C The Housenger memo lists an acute oral NOEL of 0.06 mg/kg and a chronic oral NOEL of 0.05 mg/kg. The same NOELs are given for the dermal

NOELs with the use of an 11% dermal absorption factor. The oral NOELs are also given for inhalation.

Disulfoton:

C In the August 6, 1998 document, U.S. EPA lists a NOEL of 0.1 mg/kg for maternal RBC and plasma cholinesterase inhibition and 0.3 mg/kg for developmental effects in a rat developmental toxicity study and a NOEL of 0.025 mg/kg for plasma and RBC cholinesterase inhibition and **0.1 mg/kg for pup toxicity in a rat reproduction study**.

C The Housenger memo lists an acute oral NOEL of 0.25 mg/kg and a **chronic oral NOEL of 0.013 mg/kg**. The memo lists an acute dermal NOEL of 0.4 mg/kg. Dermal intermediate and chronic NOELs of 0.03 and 0.013 mg/kg are listed for dermal, with the use of a 36% dermal absorption factor. An inhalation NOEL of 0.00016 mg/L is given for any time period.

Fenamifos:

C A Section 18 Risk Assessment was conducted by DPR in 1997. This document used a **NOEL of 0.23 mg/kg for maternal toxicity in a rabbit developmental toxicity study** as the critical NOEL for acute toxicity. The nominal NOEL in this study was 0.5 mg/kg; however, that value was adjusted to 0.23 mg/kg based on the measured instability of the material. Subchronic exposure was not addressed in this assessment. The **critical NOEL for chronic toxicity was 3 ppm (0.075 mg/kg)** for anemia and brain cholinesterase inhibition in a chronic dog study. The same NOEL was used as a default value for subchronic toxicity.

C The U.S. EPA Hazard Evaluation Division chapter for the RED on fenamiphos was completed in 1994. This document uses the unadjusted acute NOEL of 0.5 mg/kg from the rabbit developmental toxicity study. A NOEL of 1.0 ppm for plasma cholinesterase inhibition is used from two oral subchronic dog studies (stated to be equivalent to 0.025 mg/kg in one study

and 0.23 mg/kg in the other study). The critical chronic NOEL of 0.5 ppm (0.01 mg/kg) was set based on plasma cholinesterase inhibition in a chronic dog study. The NOEL for systemic effects (anemia) was 3 ppm (0.08 mg/kg).

C In addition to the values for acute toxicity and chronic toxicity used in the Section 18 risk assessment, the toxicology summary gives a NOEL of 10 ppm for reduced pup weight and a LOEL of 2.5 ppm for plasma cholinesterase inhibition in a rat reproduction study.

C In the August 6, 1998 document, U.S. EPA lists a NOEL of 0.5 mg/kg for cholinergic signs in a rabbit developmental toxicity study and a NOEL of 0.17 mg/kg for cholinesterase inhibition in a rat reproduction study.

Fonofos:

C An IRIS toxicity profile set an oral RfD of 0.002 based on a NOEL of 0.2 mg/kg for cholinesterase inhibition and cholinergic signs in a chronic dog study. A NOEL of 2 mg/kg was listed for a mouse teratology study. A NOEL of 1.58 mg/kg was listed for a rat reproduction study (no effects at any dose).

C The toxicology summary lists a **NOEL of 0.5 mg/kg for maternal toxicity in a rabbit developmental toxicity study**, a NOEL of 31.6 ppm (converted value of approximately 1.6 - 3.2 mg/kg) in an unacceptable rat reproduction study, a NOEL of 0.2 mg/kg for cholinesterase inhibition and **1.0 mg/kg for cholinergic signs in a chronic dog study**.

C In the August 6, 1998 FQPA factor document, U.S. EPA lists no NOELs and states that cancellation proceedings are in place.

Methyl bromide

C The 1992 preliminary risk assessment used an **acute NOEL of 40 ppm (21**

mg/kg) from an inhalation developmental toxicity study. This value is equivalent to an adjusted human NOEL of 21 ppm. For short term or subchronic exposure, a NOEL of 20 ppm for neurotoxicity in rabbits was used.

C The draft RCD uses the same acute values for developmental toxicity. In addition, a NOEL of 103 ppm (45 ppm human equivalent NOEL) for neurotoxicity in dogs is used. **A subchronic NOEL of 20 ppm (7 ppm human equivalent NOEL) for neurotoxicity in the rabbits was used for subchronic exposures** of shorter duration (<2 weeks). A subchronic estimated NOEL (ENEL) of 0.5 ppm (0.2 ppm human equivalent NOEL) for neurotoxicity in the dog was used for subchronic exposures of longer duration. An ENEL of 0.3 ppm (0.2 ppm human equivalent NOEL) for olfactory epithelial hyperplasia in the rat was used as the critical NOEL for chronic exposure.

MITC:

C An RCD was completed on June 17, 1998. The document has not yet undergone external peer review. The critical **acute NOEL is 220 parts per billion (ppb) (660 micrograms per liter [*u*g/L])** in the air for eye irritation in humans. The critical **subchronic NOEL is 480 *u*g/kg (1 ppm air concentration) in a 90 day rat inhalation study** for decreased body weight, increased water consumption, and decreased serum protein. Chronic exposure was not evaluated.

Oxydemeton methyl (ODM):

C The toxicology summary lists a **NOEL of 1.5 mg/kg for maternal toxicity (cholinergic signs and cholinesterase inhibition) in a rat developmental toxicity study** and a NOEL of 0.4 mg/kg for cholinesterase inhibition in a rabbit developmental toxicity study. Several rat reproduction studies were

conducted. The lowest NOEL is 1 ppm (converted level of 0.1 - 0.05 mg/kg) for reproductive effects (testicular effects) in an unacceptable study. In an acceptable **rat reproduction study, the NOEL was for testicular, ovarian, and fertility effects was 9 ppm (0.9 mg/kg)**. The summary lists a **chronic NOEL of 0.125 mg/kg for brain cholinesterase inhibition in a dog study**. A chronic NOEL of 0.57 ppm (0.057 mg/kg) is listed for cholinesterase inhibition in a chronic rat study.

C In the August 6, 1998 document, U.S. EPA lists a LOEL of 0.5 mg/kg for maternal cholinergic signs in a rat developmental toxicity study and a NOEL of 0.05 mg/kg for decreased body weight in a rat reproduction study.

C The Housenger memo lists an acute oral LOEL of 2.5 mg/kg and a chronic oral NOEL of 0.05 mg/kg. The memo lists an acute dermal NOEL of 5.0 mg/kg and an intermediate dermal NOEL of 0.3 mg/kg. The inhalation NOELs use the oral NOELs.

Permethrin:

C An RCD on permethrin (Permanone Tick Repellant®) was completed in 1994. This document set NOELs for the inhalation, oral, and dermal routes of exposure. The lowest estimated (from a LOEL) **acute inhalation NOEL was 24*u*g/ L (3.8 mg/kg) for neurological effects**. The oral NOEL (from maternal neurotoxicity in a rat developmental toxicity study) was 50 mg/kg (adjusted to an absorbed dose of 35 mg/kg). The estimated dermal NOEL was 200 mg/kg (adjusted to an absorbed dose of 50 mg/kg assuming 25% absorption).

The lowest **subchronic inhalation NOEL was equal to or greater than 500 mg/m^3 in the dog**, with no effects seen at any dose. The lowest subchronic oral NOEL was 1.7 mg/kg (liver effects) from a rat feeding study (adjusted to an absorbed dose of 1.2 mg/kg).

The lowest **chronic NOEL was 3 mg/kg (based on alveolar cell**

proliferation and liver effects) from a mouse study (adjusted to an absorbed dose of 2.1 mg/kg). While the data on oncogenic effects was not robust, DPR concluded that the oncogenic effects in mice could not be ignored and used MLE and **UB estimates of potency** of 5.7 E-3 and **7.8 x 10^{-3}** respectively based on lung tumors in the mouse.